Brit. Heart J., 1963, **25**, 741.

PULMONARY DIFFUSING CAPACITY IN MITRAL VALVE DISEASE

BY

J. M. REID AND J. G. STEVENSON

From the Department of Cardio-thoracic Surgery, Mearnskirk Hospital, Renfrewshire

Received December 8, 1962

While the pulmonary diffusing capacity is now accepted as an important test of lung function, comparatively little application of the test has been made in patients suffering from cardiac disorders. Bates, Boucot, and Dormer (1955) were the first to describe a simple and reliable means for estimating gaseous diffusion, using the steady state carbon monoxide technique. MacNamara, Prime, and Sinclair (1959) reported their results with this method in a series of normal subjects, a group of patients with emphysema, and also in a group of patients with chronic interstitial fibrosis.

The present study was designed to assess the results of diffusing capacity in patients suffering from mitral valve disease, and to attempt to correlate these results with the severity of their mitral stenosis and the degree of pulmonary hypertension present. These patients were undergoing routine appraisal for surgical treatment and, in most, complete hæmodynamic findings were available for study. As an additional measure, tests of ventilatory capacity were performed to gauge if this was impaired. In many patients with mitral stenosis there is a background of chronic bronchitis, and this by itself could interfere with the mechanics of breathing. In some of the patients in the latter part of the investigation, arterial blood gas analysis was undertaken to ascertain whether any changes in gaseous diffusion were reflected in the arterial blood.

A small group of normal healthy subjects was used as controls and a further group of patients suffering from pulmonary emphysema was similarly investigated to demonstrate how severely the pulmonary diffusing capacity could be depleted.

Methods and Subjects

A Godart pulmometer was used both for simplicity and convenience to estimate V.C. (vital capacity), M.V.V. (maximum voluntary ventilation), and F.E.V. (forced expiratory volume), while P.E.F. (peak expiratory flow) was measured by the Wright peak flow meter (Wright and McKerrow, 1959). Pulmonary diffusing capacity was assayed by the steady state carbon monoxide method after the method so fully and aptly described by MacNamara *et al.* (1959), employing a Godart diffusion test. This is a spirometric gas analyser system, with a 150-litre gas storage tank equipped with two latex balloons, one of which is inspiratory and the other expiratory. A spirometer and kymograph are connected to the circuit to record the patient's minute ventilation during the course of the test. The percentage of carbon monoxide is recorded by means of an infra-red analyser.

Arterial blood for gas analysis was obtained by direct puncture of the femoral artery. Percentage oxygen saturation was determined by means of a Kipp hæmoreflector, the CO_2 content by a manometric Van Slyke method, the *p*H by a Pye *p*H meter with a Stadie electrode (manufactured by Cambridge) and the P_{CO_2} calculated according to the Henderson-Haselbach equation $\left(P_{CO_2} = \frac{CO_2 \text{ in mEq/l.}}{S(10(pH-pK)+1)}\right)$.

Normal Controls. Seven patients free from any clinical evidence of either cardiac or respiratory disease were used as controls. The results are shown in Table I and values for the diffusing capacity (D_{CO}) both at rest and following exercise are in close accord with those of MacNamara

et al. (1959). Those authors found in normal subjects mean values of 23·3 ml./min./mm. Hg at rest and 32·5 ml./min./mm. Hg on exercise. Filley, MacIntosh, and Wright (1954) recorded mean values of 16·9 at rest and 36·3 on exercise in 11 healthy subjects.

Eleven patients with clinical and radiological evidence of *diffuse pulmonary emphysema* were examined and the data are recorded in Table II.

TABLE I

SEVEN NORMAL SUBJECTS

V.C. (ml.)	M.V.V. (l./min.)	P.E.F. (l./min.)	F.E.V. % (1 sec.)	D_{CO} at rest (ml./min./mm. Hg)	D_{CO} at exercise (ml./min./mm. Hg)
3000	90	450	80	14	27
3700	100	400	72	11	23
4000	125	430	80	16	25
2700	80	380	—	23	38
2600	100	450	—	22	36
3500	90	370	—	30	39
3000	80	320	72	19	27

TABLE II

ELEVEN PATIENTS WITH PULMONARY EMPHYSEMA

V.C. (ml.)	M.V.V. (l./min.)	P.E.F. (l./min.)	F.E.V. % (1 sec.)	D_{CO} at rest (ml./min./mm. Hg)	D_{CO} at exercise (ml./min./mm. Hg)
2000	40	100	57	8	9
1800	40	80	66	8	9
1200	15	100	—	8·6	10·5
750	15	90	—	9	11
500	10	100	—	7	11
1500	15	170	—	14	10·5
1000	15	80	—	13	16
2500	63	390	64	16	19
1000	30	220	80	16	16
1700	50	300	72	6	5
2500	55	160	58	8·5	7

Patients with Mitral Valve Disease. There were 53 patients, 45 of whom were women and only 8 men. Their ages ranged from 21 to 57 years, and all were undergoing routine investigation or possible surgical relief of their mitral stenosis. All had, without exception, symptoms attributable to their mitral disease, the principal one being exertional dyspnœa, varying in severity from Grade I to IV. In addition, seven had a history of recurrent attacks of bronchitis. Many patients with established mitral stenosis have a background of chest trouble, due principally to pulmonary congestion, and this manifests itself by recurring wheeziness and blood-streaking of the sputum. The condition referred to in the seven patients above, however, was considered to be a separate entity unrelated to their cardiac state. The significance of this emerges later when considering the results of their lung function tests, particularly those of ventilation.

Pulmonary arterial pressure was measured either at operation or during right heart catheterization, and in the latter instance pulmonary vascular resistance and cardiac output were also calculated. Of the 53 patients under discussion, 7 were not operated on for the following reasons: dominant mitral regurgitation (5); gross pulmonary emphysema (1); and death from acute right heart failure quite suddenly while awaiting operation (1). In the remainder pressures were recorded in left ventricle, pulmonary artery, and left atrium, both before and after valvotomy.

In addition, the size of the mitral valve orifice was measured at operation and this was used as an index of the severity of the stenosis.

RESULTS

Fig. 1 correlates in graphic form the size of the mitral orifice as measured at operation, with the pulmonary diffusing capacity both at rest and on exercise.

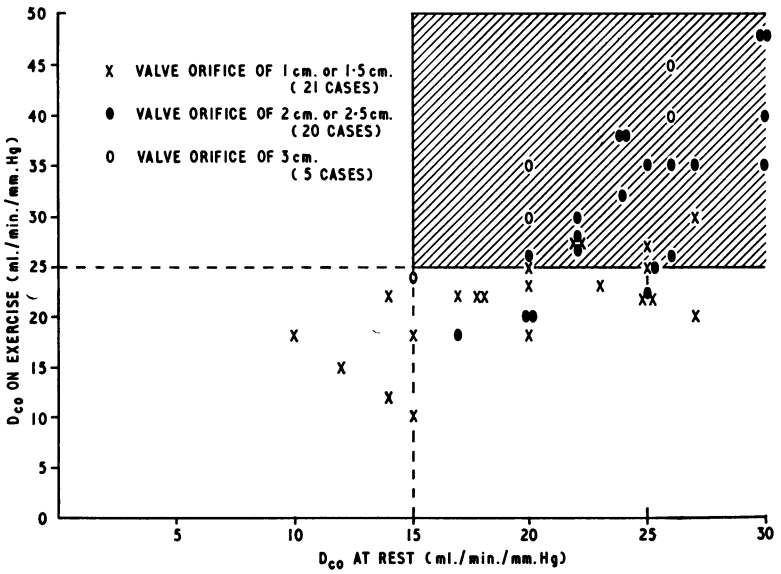

FIG. 1.—D_{CO} at rest and exercise correlated with valve size. Shaded area denotes normal range for D_{CO} at rest and on exercise.

Those with very tight valve orifices (1 cm. or less) had, by and large, a diffusing capacity that was either low normal or just below the normal at rest, and little increase followed exercise. With increasing valve size the diffusing capacity approximated more closely to normal at rest and showed a significant augmentation with exercise.

In Table III the patients are divided into five grades according to the systolic pressure recorded in the pulmonary artery.

TABLE III

NUMBER IN EACH GRADE (SYSTOLIC PRESSURE IN PULMONARY ARTERY IN MM. HG)

15–30 mm.	31–45 mm.	46–60 mm.	61–75 mm.	76–100 mm.
9	9	13	10	12

Fig. 2 correlates pulmonary arterial pressure with the D_{CO} at rest and on exercise. In nine patients with normal pulmonary arterial pressure, the D_{CO} was well within the normal range. Conversely, at the other end of the scale, those with severe pulmonary hypertension (systolic pressure of 61 mm. Hg or above) showed considerable impairment of the D_{CO}.

Table IV presents the hæmodynamic findings in the seven patients with mitral stenosis and accompanying chronic bronchitis. Three of those with chronic bronchitis showed subnormal results for D_{CO} at rest and in none of the seven was there any substantial rise with exercise. In four of the five who were operated on, the size of the mitral orifice was at a critical level. Pulmonary hypertension was present in all but one.

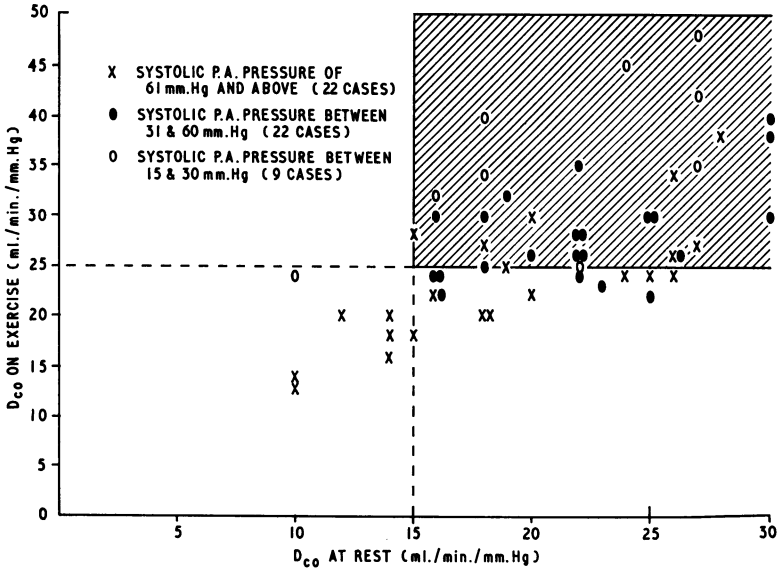

FIG. 2.—D_{CO} at rest and exercise correlated with P.A. pressure. Shaded area denotes normal range for D_{CO} at rest and on exercise.

TABLE IV

SEVEN PATIENTS WITH MITRAL STENOSIS AND CHRONIC BRONCHITIS

V.C. (ml.)	P.A. pressure (mm. Hg)	D_{CO} at rest (ml./min./mm. Hg)	D_{CO} at exercise (ml./min./mm. Hg)	Valve (cm.)
1500	75/30	24	—	1
1000	100/50	20	12	—*
2800	27/12	24	18	2·5
1200	75/50	12	15	—†
2300	50/25	20	26	1·5
2000	75/50	15	14	1·5
1500	70/45	13	15	1·5

* This patient was not operated on because of severe pulmonary emphysema.
† This patient died while awaiting operation.

While chronic bronchitis *per se* does not reduce the D_{CO}, the latter will be decreased when there is accompanying pulmonary emphysema, due principally to an encroachment by tissue destruction on the available surface area for diffusion. In the group under discussion the low D_{CO} could be due either to the severity of the mitral obstruction with the accompanying hæmodynamic changes in the pulmonary circulation, to the degree of pulmonary emphysema with the consequent reduction in the number of functioning alveoli, or perhaps to a combination of both.

Arterial Blood Gas Analysis. This was carried out in 17 of the patients with mitral valve disease, and in 6 of these a venous sample was also obtained for analysis. The arterial *p*H ranged from 7·32 to 7·42 and the venous from 7·29 to 7·40, both values being well within the normal scale. Arterial CO_2 content varied from 20·8 mEq per litre to 27 mEq per litre, while the P_{CO_2} values fell within the normal range of 36·2 to 44·9 mm. Hg. Percentage arterial oxygen saturation averaged 94, although in one patient the saturation was only 82 per cent. In this patient there was severe concomitant bronchitis, as a result of which ventilatory function was severely depleted (V.C. 1500 ml., M.V.V. 37 l. per min., P.E.F. 150 l. per min.). The D_{CO} was 13 ml. per min. per mm. Hg at

rest, rising to only 15 with exercise. The resting pulmonary arterial pressure was 70/45 mm. Hg, and at operation the size of the valve orifice was found to be 1·5 cm.

Ventilatory Capacity. There was evidence of impaired V.C. in 23 of the patients with mitral disease, as judged by the presence of two or more of the following criteria: a vital capacity of 2200 ml. or less, an M.V.V. of 50 l. or less, or a P.E.F. lower than 200 l. Five patients who fulfilled these requirements had accompanying bronchitis and the reduction in ventilatory function could be explained simply on this basis alone. However, in the remaining 18, some other factor or factors must be considered. The majority of them had moderate or severe pulmonary hypertension, and most had critical or near critical obstruction of the mitral valve.

Discussion

The diffusing capacity of the lungs is governed by two principal factors, the permeability of the diffusing surface, and the area available for diffusion. Roughton and Forster (1957) demonstrated that it was also influenced by the volume of blood in ventilated capillaries. MacNamara, Prime, and Sinclair (1960) showed conclusively that the observed rise in D_{CO} with exercise was due to an increase in the area of capillary wall exposed to alveolar gas. This is produced partly by hyperventilation and also by augmentation of cardiac output.

In established mitral stenosis cardiac output at rest is low and little increase can occur with exercise due to the impediment to venous return to the left atrium. In the early stage of mitral stenosis the left atrium passively dilates and its pressure rises in an effort to overcome the obstruction. The severity of the diastolic gradient across the mitral valve at this point is a measure of the degree of narrowing of the valve. At a later stage the raised pressure in the left atrium is reflected back into the pulmonary circulation and pulmonary congestion is added to this vicious circle. However, progression of the disease leads to gradual narrowing of the pulmonary vasculature, with commencing rise in pulmonary vascular resistance. The lungs are by now becoming rigid and losing their normal elasticity and compliancy.

Carroll, Cohn, and Riley (1953) studied 29 patients suffering from varying degrees of obstruction of the mitral valve. In the patients with early disease there was hardly any interference with pulmonary ventilation, circulation, distribution, or gaseous diffusion. With more severe obstruction they found that changes could occur in either diffusion or distribution or in both, and they postulated that such alterations might be either structural or functional in character.

In the 53 patients with mitral stenosis in the present study, the changes found both in diffusing capacity and ventilatory function can be correlated with the pathological changes outlined above. Most of those with established pulmonary hypertension had sub-normal values for D_{CO} particularly on exertion. The explanation for this is that although under the physiological response to exercise the pulmonary blood flow can still be augmented, no increase can occur in the area for blood gas exchange due to the existence of pulmonary congestion. At a more advanced stage of the disease, other factors begin to operate. The cardiac output becomes progressively diminished and there is a reduction in the pulmonary blood flow associated with narrowing of the pulmonary vessels. This inevitably results in impairment in gaseous diffusion. Ultimately, in addition to these changes, the alveolar membrane becomes thickened. Interstitial œdema develops and there is commencing fibrosis of the interstitium. These eventually, in combination, produce permanent lung damage with raised pulmonary vascular resistance. The D_{CO} will now not only fail to rise with exercise, but will also be sub-normal at rest. Loss of the normal elasticity and compliancy of the lungs will be reflected in depletion of ventilatory function.

In this series 18 patients belonged to this latter category and the P.V.R. was found to be above the normally accepted level (one to two units). In two patients the resistance was as high as 12 units. The single operative death that occurred during the study was in a patient who belonged to this group. He was a man of 50 years with Grade IV dyspnœa and severe disability. The resting pressure in his pulmonary artery was 90/50 and the P.V.R. was more than 10 units, and the vital capacity was 1750 and D_{CO} was 14 and 17 ml./min./mm. Hg respectively at rest and on exercise:

at operation the mitral orifice was found to be less than 1 cm., and although a satisfactory valvotomy was performed, death occurred 24 hours later from cardio-respiratory failure.

In five patients with concomitant bronchitis that was considered to be a separate entity, there was gross impairment of ventilatory function and severe encroachment on diffusing capacity. All five had considerable pulmonary hypertension with severe mitral stenosis. However, in addition to the factors alluded to above, their disability was attributable, in large measure, to the accompanying pulmonary emphysema. MacNamara *et al.* (1959) contended that the decreased D_{CO} in pulmonary emphysema was due to reduction in the capillary bed by tissue destruction and also to uneven alveolar ventilation. Apart from any permanent tissue damage, bronchospasm by itself can depress the D_{CO} as demonstrated by Lorriman (1959).

Manifestly, the D_{CO} is closely related to the pulmonary blood flow. Where this is increased, as in intracardiac septal defects without significant pulmonary hypertension, the D_{CO} is raised at rest (Auchincloss, Gilbert, and Eich, 1959). Once pulmonary hypertension becomes established, however, in these cases with intracardiac shunts, the D_{CO} falls despite continuation of the high pulmonary blood flow. This phase represents commencing damage to the alveolar capillary membrane related to vascular obstruction. The same authors observed normal or reduced values for D_{CO} in mitral stenosis, but they did not attempt to correlate these with valve size, severity of the obstruction, or the presence of coexistent lung disease. Their hypothesis that a reduced D_{CO} in mitral disease is indicative of permanent lung damage is not altogether tenable in every case. If a satisfactory valvotomy is performed with reduction in pulmonary arterial pressure, relief of the obstruction, and disappearance of pulmonary congestion, the D_{CO} must inevitably improve. Only in those cases of advanced disease with raised pulmonary vascular resistance and rigid lungs is the impaired D_{CO} due mainly to permanent lung damage.

In the present series, gas analysis of the arterial blood showed abnormality in only one instance, namely an oxygen saturation of 82 per cent. This patient, however, had advanced pulmonary emphysema in addition to mitral stenosis and it seems highly probable that this, rather than the mitral disease, was the cause of the arterial oxygen desaturation.

Summary and Conclusions

The results of tests of both ventilatory and diffusing capacities in 53 patients with mitral valve disease are presented and these have been correlated with the size of the mitral orifice found at operation and with the pulmonary arterial pressure.

The tests were also performed in 7 normal subjects as controls and also in 11 patients with no cardiac disease but with severe pulmonary emphysema, to indicate how severely the D_{CO} could be reduced.

The present study confirms that in early mitral disease with no rise in pulmonary arterial pressure and no demonstrable pulmonary congestion, ventilation is normal as is the D_{CO} at rest and on exercise. With the onset of pulmonary hypertension and consequent reduction in pulmonary blood flow, the D_{CO} fails to show the normal physiological increase with exercise. At a more advanced stage of the disease, when definitive pulmonary vascular changes are present, which may or may not be reversible, the D_{CO} is also low at rest. In addition, the impaired ventilatory capacity reflects the loss of compliancy by the lungs.

The work was carried out in the Cardio-thoracic Unit at Mearnskirk Hospital, and all the operations were performed by Mr. R. S. Barclay and Mr. T. M. Welsh. Dr. Anderson and his biochemical staff were responsible for the blood gas analysis, and to them the authors are deeply indebted.

References

Auchincloss, J. H., Jr., Gilbert, R., and Eich, R. H. (1959). The pulmonary diffusing capacity in congenital and rheumatic heart disease. *Circulation*, **19**, 232.

Bates, D. V., Boucot, N. G., and Dormer, A. E. (1955). The pulmonary diffusing capacity in normal subjects. *J. Physiol. (Lond.)*, **129**, 237.

Carroll, D., Cohn, J. E., and Riley, R. L. (1953). Pulmonary function in mitral valvular disease: Distribution and diffusion characteristics in resting patients. *J. clin. Invest.*, **32**, 510.

Filley, G. F., MacIntosh, D. J., and Wright, G. W. (1954). Carbon monoxide uptake and pulmonary diffusing capacity in normal subjects at rest and during exercise. *J. clin. Invest.*, **33**, 530.

Lorriman, G. (1959). The effects of bronchodilators on pulmonary ventilation and diffusion in asthma and emphysema. *Thorax*, **14**, 146.

MacNamara, J., Prime, F. J., and Sinclair, J. D. (1959). An assessment of the steady-state carbon monoxide method of estimating pulmonary diffusing capacity. *Thorax*, **14**, 166.

——, ——, and —— (1960). The increase in diffusing capacity of the lungs on exercise. An experimental and clinical study. *Lancet*, **1**, 404.

Roughton, F. J. W., and Forster, R. E. (1957). Relative importance of diffusion and chemical reaction rates in determining rate of exchange of gases in the human lung. *J. appl. Physiol.*, **11**, 290.

Wright, B. M., and McKerrow, C. B. (1959). Maximum forced expiratory flow rate as a measure of ventilatory capacity: with a description of a new portable instrument for measuring it. *Brit. med. J.*, **2**, 1041.